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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : G01N 33/49, 33/86 — A1

(11) International Publication Number: **WO 97/41432**

(43) International Publication Date: 6 November 1997 (06.11.97)

(21) International Application Number: PCT/US97/07356

(22) International Filing Date: 30 April 1997 (30.04.97)

(30) Priority Data:
08/640,277 30 April 1996 (30.04.96) US

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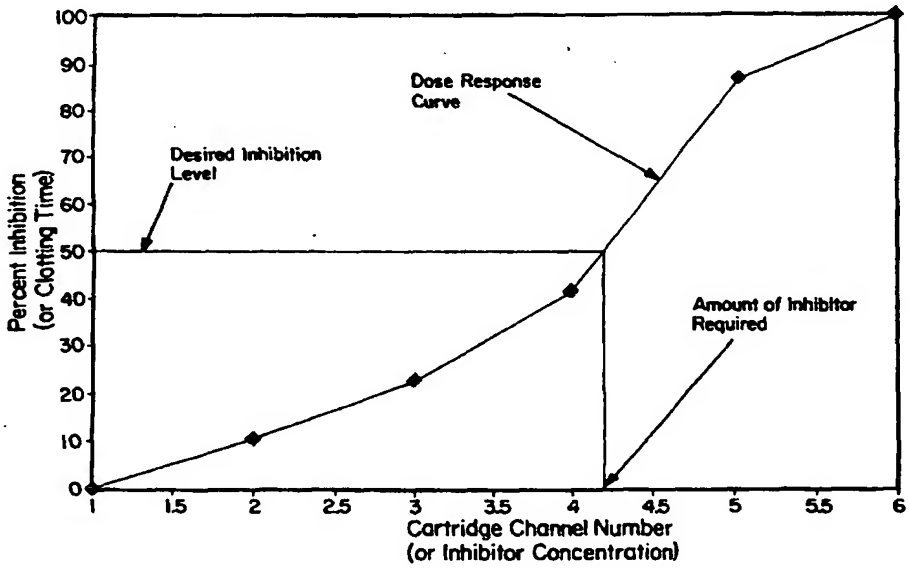
(81) Designated States: DE, JP.

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD FOR DETERMINING PLATELET INHIBITOR RESPONSE



(57) Abstract

A method of determining a dose response for a platelet inhibitor. The method includes the steps of placing a predetermined amount of heparin in each cell of a multicell test cartridge, placing an optimized amount of a clotting activator in each cell, and placing a measured amount of platelet inhibitor in each cell, the amount of inhibitor in each cell differing from the amount in each other cell. An aliquot of a blood sample is added to each cell, and the blood sample aliquot, clotting reagent and platelet inhibitor are mixed. Each cell sample is allowed to clot, and the clotting time for each cell is measured. The relative clotting times are used to calculate and determine the platelet inhibition effect of the platelet inhibitor.

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METHOD FOR DETERMINING PLATELET INHIBITOR RESPONSE

Description

Technical Field

The present invention relates to measuring and determining the effectiveness of antiplatelet reagents or platelet inhibitors in the coagulation of blood.

More specifically, the present invention relates to a method of determining the effectiveness of antiplatelet reagents or platelet inhibitors on the mechanical activation of platelets.

Background Art

U.S. Pat. No. 5,174,961 and U.S. Pat. No. 5,314.826 describe clotting tests which measure the ability of various drugs and pharmacological agents to inhibit the normal functions of platelets. The method and apparatus described performs six, four or two channel coagulation tests of which there are a number of variants. In particular, the electromechanical assembly in the instrument which lifts and lowers the flag-plunger assembly (described in Pat. No. 4,599,219) in each channel of the assay cartridge, is under software control. The rate at which the flag-plunger assembly is lowered through the whole blood assembly can thus be controlled. Pat. No. 5,314,826 describes how the rate at which the flag-plunger assembly is lowered through a whole blood sample affects the rate at which platelets are activated. The description of what happens in the blood sample can be described as follows. Slowly lowering the flag-plunger assembly leads to the generation of low shear forces within the blood sample. Under these conditions the platelets in the blood sample rapidly activate in which they expose platelet factor 3 activity and possibly release platelet factor 4 activity. Under the conditions of the assay, activation of both of these components will shorten the blood clotting time.

If the shear rate in the blood sample is changed to higher shear forces by increasing the fall rate of the flag-plunger, the ability of the platelets to rapidly activate clotting is impaired and the clotting time becomes longer. The postulated mechanism is that the platelets bind to the kaolin or clotting reagent particles used the trigger contact activation. Once the platelets bind to the kaolin particles, they are activated, which leads to an increase in the rate at which the blood clots.

U.S. Pat. No. 5,314,826 compares the clotting times of a blood sample under the two extreme conditions, maximal (or low shear force) activation and minimal (or high shear force). This is referred to as measuring platelet activity using mechanical platelet activation. The degree of mechanical activation achieved is related to the amount of time the blood sample is subjected to this low shear force condition. The longer the mechanical activation period, the shorter the clotting time. Under the conditions in which an activated clotting time test is performed (the basic blood clotting test for measuring the contribution of platelets to coagulation), the activation of platelets is a rate limiting step, i.e., the actual clotting times depend on how rapidly the platelets are able to activate clotting. As such, any additive which can accentuate this rate limited step can be added to the test sample and the effect is even more noticeable. In this case, heparin is added to the assay

sample. Heparin inhibits other factors in coagulation so that the effect of platelets on coagulation is even more noticeable.

While it is known that antiplatelet drugs or compounds inhibit the activation of platelets, Pat. No. 5,314,826 does not address the use of a mechanical activation cycle to optimize an assay for determining the impact of platelet inhibitors.

It is the principal object of the present invention to provide an improved method for measuring and determining the effectiveness of antiplatelet reagents or platelet inhibitors on the coagulation of blood.

Brief Description of the Drawings

Fig. 1 is a hypothetical graph of Percent Inhibition vs. Inhibitor Concentration.

Disclosure of Invention

In accordance with the foregoing objects, the present invention is embodied in a method of determining a dose response for a platelet inhibitor. The method includes the steps of placing a predetermined amount of heparin in each cell of a multicell test cartridge, placing an optimized amount of a clotting activator in each cell, and placing a measured amount of platelet inhibitor in each cell, the amount of inhibitor in each cell differing from the amount in each other cell. An aliquot of a blood sample is added to each cell, and the blood sample aliquot, clotting reagent and platelet inhibitor are mixed. Each cell sample is allowed to clot, and the clotting time for each cell is measured. The relative clotting times are used to calculate and determine the platelet inhibition effect of the platelet inhibitor.

Best Mode for Carrying out the Invention

In accordance with the present invention, it has been discovered that the ability of platelet inhibitors or antiplatelet drugs to effect coagulation of blood can be readily assessed. To this end, by using different concentrations of a platelet inhibitor in a plurality of test cells, and using a standard optimized mechanical activation cycle the ability of an inhibitor in a selected dose to prevent the mechanical activation of platelets can be assessed.

The performance of a dose response test in accordance with the present invention embodies the following steps:

1. A six channel assay cartridge is selected and a predetermined amount of heparin (1-3 units/ml) is placed in each cartridge cell to enhance the sensitivity of the assay.

2. An optimized amount of an activator solution, kaolin plus buffer and stabilizers, for showing the effect of platelets on an activated clotting time, is placed in the reagent portion of each cell. Amounts of 12% and 10% kaolin have been used. One illustrative composition is HEPES buffer, 5OmM calcium chloride, .02% sodium azide as a bacteriostatic agent, and 10% kaolin, at pH 7.4. The buffer is isotonic with respect to sodium chloride.

3. A platelet inhibitor is added to the reaction chambers or cells of the assay cartridge

in the following concentrations:

Cell 1	None
Cell 2	None
Cell 3	X
Cell 4	aX
Cell 5	bX
Cell 6	cX

The actual concentrations cannot be given until a specific antiplatelet compound is tested in the system. X represents a low concentration of the compound with which inhibition (or an increase in the clotting time) is just noticeable. Factors a, b, and c represent multiple increases in the amount of the compound x added to the cells. Concentration cX is preferably an excess of the compound, in order to give maximal inhibition of platelet activation. Increasing the amount of the antiplatelet drug above this concentration will not further increase the clotting time.

4. The assay cartridge apparatus is programmed for an appropriate mix cycle and sample volume.

5. A blood sample is drawn and aliquot volumes of the sample (0.35ml) are dispensed into each of the six cells of the assay cartridge.

6. The test is initiated by injecting the contents of the reagent chamber into the reaction chamber of each test cell.

7. The above action mixes the reagent and platelet inhibitor, if any, with the blood sample.

8. The "mixing cycle" is run for a predetermined period of time, about 8 to 60 seconds.

9. At the termination of the "mix cycle," the agitator is switched to a drop rate in the high shear force mode. This optimizes the ability to detect clot formation. Clotting time is then measured for the sample in each cell.

10. When all six cells have clotted, the test is terminated and a relative clotting time is computed wherein the clotting times of the cells containing no platelet inhibitor are used as the reference clotting time. The simplest calculation is to consider this zero percent inhibition, and the cell with the maximum amount or excess of the inhibitor is considered as 100% inhibition. The clotting times from the intermediate cells are then compared to determine the dose response.

The purpose of the foregoing test is three-fold: 1) to determine an individual's basic response to the platelet inhibitor, 2) to monitor the presence of the platelet inhibitor, and 3) to determine the quantitative concentration of the inhibitor.

To illustrate the use of the present invention, a dose response cartridge test is performed on a patient using compound x as a specific platelet inhibitor. A titration curve is plotted which is used to compute a dosage of the drug which will be given to the patient. The test apparatus

computes this dosage based on the clotting times and the program which relates to this specific drug. After giving the patient the drug, a two channel activated clotting time assay is performed. This measures whether or not the target clotting time has been achieved and is a measure of the effectiveness of the drug.

If a specific concentration of the drug is desired, this may be determined by using the previous dose response curve obtained to compute the concentration of the inhibitor. Alternatively, if a chemical or antibody exists which will neutralize the platelet inhibitor, the concentration of the platelet inhibitor can be determined using a titration cartridge containing varying amounts of the neutralizing chemical.

Fig. 1, illustrates a process in which the desired degree of platelet inhibition is a 50% inhibition. The Y-axis is computed from the clotting times obtained using the above-described dose response assay cartridge. The clinician enters the 50% inhibition figure into the apparatus and the apparatus computes the information given in Fig. 1. Using Fig. 1, the horizontal line labeled "Desired Inhibition Level" represents 50% inhibition. This line intersects the "Dose Response Curve." A vertical line is dropped from this point of intersection to the X-axis where the intersection of the line with the X-axis provides the concentration of inhibitor required to achieve 50% inhibition of the platelets. Fig. 1 is labeled in terms of cell numbers, but could also be labeled with concentrations of the inhibitor, from zero in cell 1 to the maximum (100% inhibition) in cell 6.

In monitoring the effectiveness of the drug, the above dose response curve can be used after running a two channel assay cartridge, taking the clotting time (the Y- axis could also be given in terms of the clotting times rather than a percentage of inhibition). This is used to convert the clotting time to a concentration of the inhibitor using the same type of calculation as above.

A third method for determining the amount of platelet drug present uses a titration assay. This requires that a chemical or antibody capable of neutralizing the inhibitor be available. In a titration cartridge, each channel of the assay cartridge contains increasing amounts of the neutralizing agent. The channel where the shortest clotting time is obtained is the concentration of neutralizing agent where all of the platelet inhibitor has been neutralized. Knowing the stoichiometry between the neutralizing agent and the platelet inhibitor, the concentration of the platelet inhibitor present in the sample can be computed.

While an illustrative embodiment of the present invention has been described above in considerable detail, it should be understood that there is no intention to limit the invention to the specific embodiment disclosed. On the contrary, the intention is to cover all modifications, alternatives, equivalents and uses falling within the spirit and scope of the invention as expressed in the appended claims.

Claims

1. A method of determining a dose response for a platelet inhibitor comprising the steps of placing a predetermined amount of heparin in each cell of a multicell test cartridge, placing an optimized amount of a clotting activator in each said cell, placing a measured amount of platelet inhibitor in each said cell, the amount of inhibitor in each cell differing from the amount in each other cell, adding an aliquot of a blood sample to each said cell, mixing said blood sample aliquot, clotting reagent and platelet inhibitor, clotting each cell sample and measuring the clotting time for each said cell, and computing the relative clotting times to determine the platelet inhibition effect of the platelet inhibitor.

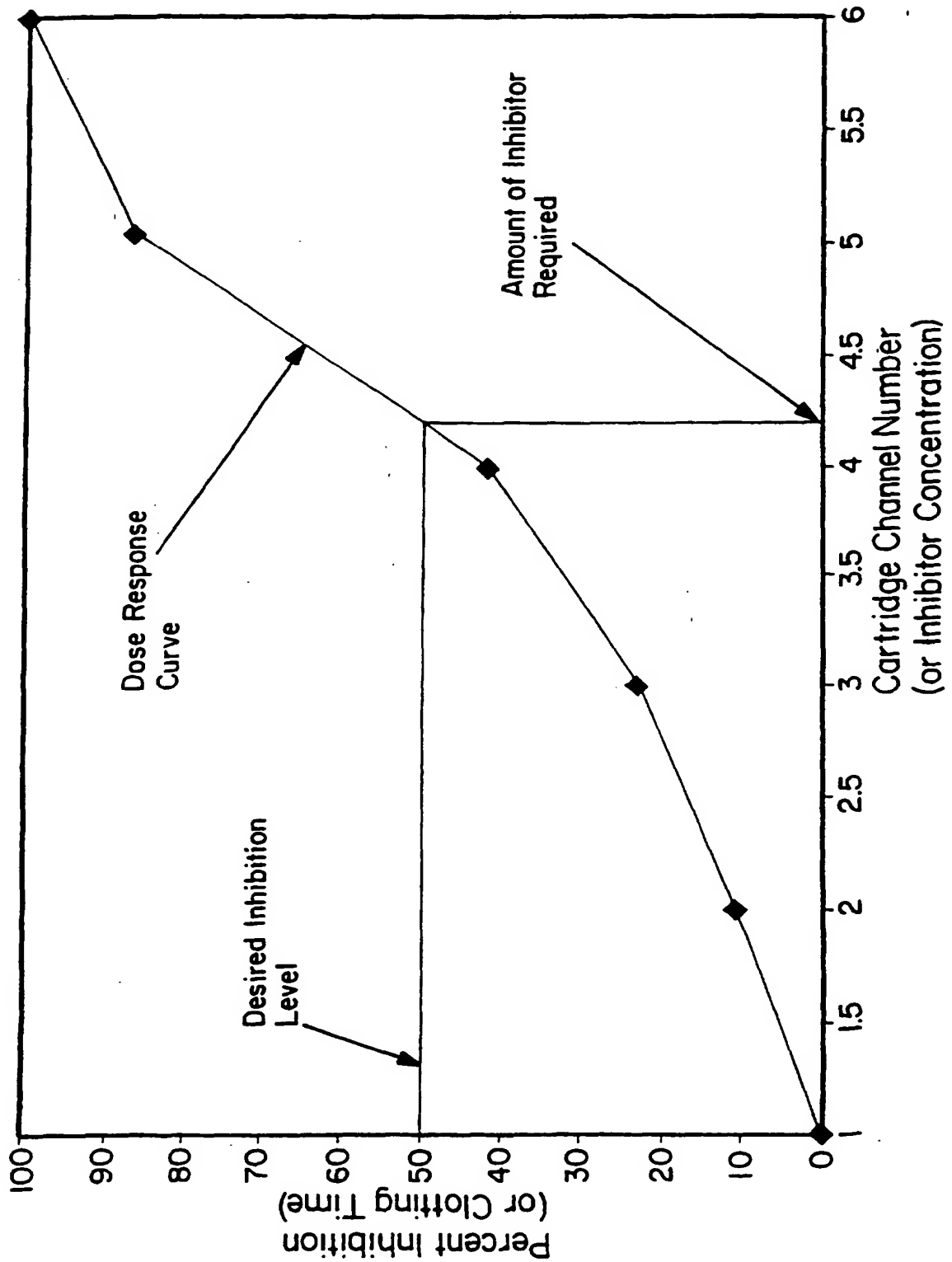
Percent Inhibition
(or Clotting Time)
0
10
20
30
40
50
60
70
80
90
100
Cartridge Channel Number
(or Inhibitor Concentration)
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
Dose Response
Curve
Desired Inhibition
Level
Amount of Inhibitor
Required

FIG. 1

INTERNATIONAL SEARCH REPORT

Inte .onal Application No
PCT/US 97/07356

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N33/49 G01N33/86

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 314 826 A (BAUGH ROBERT F) 24 May 1994 cited in the application see abstract	1
A	US 4 599 219 A (COOPER DANIEL ET AL) 8 July 1986 cited in the application see abstract	1
A	EP 0 661 383 A (BEHRINGWERKE AG) 5 July 1995 see abstract	1
A	WO 93 25578 A (DEPARTMENT OF THE ARMY U S GOV) 23 December 1993 see abstract; claim 1	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 August 1997	05.09.97

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ·onal Application No
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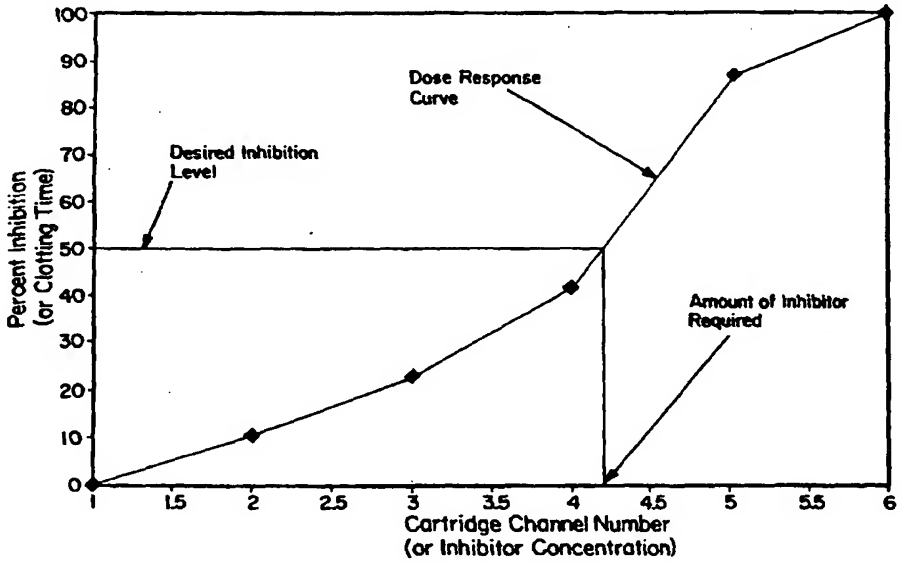
(81) Designated States: DE, JP.

Published
With international search report.
With amended claims.
Date of publication of the amended claims:
18 December 1997 (18.12.97)

(54) Title: METHOD FOR DETERMINING PLATELET INHIBITOR RESPONSE



(57) Abstract

A method of determining a dose response for a platelet inhibitor. The method includes the steps of placing a predetermined amount of heparin in each cell of a multicell test cartridge, placing an optimized amount of a clotting activator in each cell, and placing a measured amount of platelet inhibitor in each cell, the amount of inhibitor in each cell differing from the amount in each other cell. An aliquot of a blood sample is added to each cell, and the blood sample aliquot, clotting reagent and platelet inhibitor are mixed. Each cell sample is allowed to clot, and the clotting time for each cell is measured. The relative clotting times are used to calculate and determine the platelet inhibition effect of the platelet inhibitor.

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AMENDED CLAIMS

[received by the International Bureau on 28 October 1997 (28.10.97);
claims 2-32 added; remaining claim unchanged (4 pages)]

1. A method of determining a dose response for a platelet inhibitor comprising the steps of placing a predetermined amount of heparin in each cell of a multicell test cartridge, placing an optimized amount of a clotting activator in each said cell, placing a measured amount of platelet inhibitor in each said cell, the amount of inhibitor in each cell differing from the amount in each other cell, adding an aliquot of a blood sample to each said cell, mixing said blood sample aliquot, clotting activator and platelet inhibitor, clotting each cell sample and measuring the clotting time for each said cell, and computing the relative clotting times to determine the platelet inhibition effect of the platelet inhibitor.

2. A method as defined in claim 1, wherein the amount of heparin in each cell is between about 1 unit and about 3 units per milliliter of blood sample.

3. A method as defined in claim 1, wherein the clotting activator is kaolin.

4. A method as defined in claim 1, wherein the amount of clotting activator in each cell is between about 10 percent and about 12 percent.

5. A method for performing an activated clotting time test on a sample of blood containing platelets, said method comprising the steps of:

combining an anticoagulant, a clotting activator, a platelet inhibitor, and the sample of blood to be tested to form a test mixture at the start of the activated clotting time test;

activating the platelets of the sample by agitating the test mixture;

terminating the activated clotting time test upon detecting a predetermined change in a property of the test mixture; and

calculating the activated clotting time of the sample of blood based on the elapsed time.

6. A method as defined in claim 5, wherein the anticoagulant is heparin.

7. A method a defined in claim 6, wherein the amount of heparin in each cell is between about 1 unit and about 3 units per milliliter of blood sample.

8. A method as defined in claim 5, wherein the clotting activator is kaolin.

9. A method as defined in claim 5, wherein the amount of clotting activator in each cell is between about 10 percent and about 12 percent.

10. A method for determining a dose response to an antiplatelet compound in a sample of blood containing platelets using a coagulation detection apparatus, said apparatus comprising a first, a second and a third test cell, each of said cells comprising an anticoagulant and a clotting

activator, wherein said first cell further comprises a first amount of said antiplatelet compound, and wherein said second cell comprises a second amount of said antiplatelet compound, said first and second amounts being different, and method comprising the steps of:

dividing the sample of blood into first, second and third partial samples;

dispensing the first partial sample into the first test cell to form a first test mixture;

performing a first activated clotting time test on the first text mixture to obtain a first clotting time;

repeating the aforementioned steps of dispensing and performing an activated clotting time test on each of said and third partial samples to obtain a second and third clotting time; and

comparing the activated clotting times of he first, second, and third partial samples to determine a dose response to the antiplatelet compound.

11. A method as defined in claim 10, wherein the first amount of said antiplatelet compound is an amount sufficient to achieve maximal inhibition of platelet activation.

12. A method as defined in claim 10, wherein the second amount of said antiplatelet compound is an amount approximately intermediate between zero and the first amount of said antiplatelet compound.

13. A method as defined in claim 10, wherein the comparing step further comprises preparing a titration curve by plotting the activated clotting times of the first, second, and third partial samples.

14. A method as defined in claim 10, wherein the anticoagulant is heparin.

15. A method as defined in claim 14, wherein the amount of heparin in each cell is between about 1 unit and about 3 units per milliliter of blood sample.

16. A method as defined in claim 10, wherein the clotting activator is kaolin.

17. A method as defined in claim 16, wherein the amount of kaolin in each cell is between about 10 percent and about 12 percent.

18. A method for determining the concentration of an antiplatelet compound in a sample of blood using a coagulation detection apparatus, said apparatus comprising a first, a second and a third test cell, each of said cells comprising an anticoagulant and a clotting activator, wherein said first cell further comprises a first amount of a neutralizing agent capable of neutralizing the antiplatelet compound, and wherein said second cell further comprises a second amount of said neutralizing agent, said first and second amounts being different, said method comprising the steps of:

dividing the sample of blood in first, second and third partial samples;

dispensing the first partial sample into the first test cell to form a first test mixture;

performing a first activated clotting time test on the first test mixture to obtain a first clotting time;

repeating the aforesaid steps of dispensing and performing an activated clotting time test on each of said second and third partial samples to obtain a second and third clotting time; and

comparing the activated clotting times of the first, second, and third partial samples to determine the concentration of the antiplatelet compound in the sample of blood.

19. A method as defined in claim 18, wherein said neutralizing agent is a chemical or an antibody.

20. A method as defined in claim 18, wherein the comparing step further comprises preparing a titration curve by plotting the activated clotting times of the first, second, and third partial samples.

21. A method for determining a dosage of an antiplatelet drug to be administered to a patient to provide a desired degree of platelet inhibition in said patient, wherein said method uses a coagulation detection apparatus, said apparatus comprising a first, a second and a third test cell, each of said cells comprising an anticoagulant and a clotting activator, wherein said first cell further comprises a first amount of said antiplatelet drug, and wherein said second cell further comprises a second amount of said antiplatelet drug, said first and second amounts being different, said method comprising the steps of:

taking a sample of the patient's blood; and

performing a platelet inhibition test on the sample of blood, and platelet inhibition test further comprising:

dividing the sample of blood into first, second and third partial samples;

dispensing the first partial sample into the first test cell to form a first test mixture;

performing a first activated clotting time test on the first test mixture to obtain a first clotting time;

repeating the aforementioned steps of dispensing and performing an activated clotting time test on each of said second and third partial samples to obtain a second and third clotting time; and

comparing the activated clotting times of the first, second, and third partial samples to determine the dosage of the antiplatelet drug to be administered to the patient to provide the desired degree of platelet inhibition in the patient.

22. A method as defined in claim 21, wherein the first amount of said antiplatelet drug is an amount sufficient to achieve maximal inhibition of platelet activation.

23. A method as defined in claim 21, wherein the second amount of said antiplatelet drug is an amount approximately intermediate between zero and the first amount of said antiplatelet drug.

24. A method as defined in claim 21, wherein the comparing step further comprises preparing a titration curve by plotting the activated clotting times of the first, second, and third partial samples.

25. A method as defined in claim 21, further comprising:

administering the dosage of the antiplatelet drug to the patient based on the comparison of the activated clotting times of the first, second, and third partial samples.

26. A method as defined in claim 25, further comprising diagnosing the effectiveness of the antiplatelet drug by steps comprising:

taking an additional sample of the patients blood after the step of administering the antiplatelet drug; and

repeating the aforementioned steps using the additional sample to determine the degree of platelet inhibition as a result of administering the antiplatelet drug.

27. An apparatus for performing a platelet inhibition test on a sample of blood, said apparatus comprising a plurality of test cells, said cells being adapted for receiving an aliquot portion of said sample, wherein each of said cells comprises an anticoagulant and a clotting activator, and wherein at least one of said cells further comprises a platelet inhibitor, and whereby a clotting time is determined for each of said aliquot portions, and wherein a relative clotting time for each of said aliquot portions comprising the platelet inhibitor is determined as compared to a reference clotting time for a cell containing no platelet inhibitor, wherein said relative clotting times in said cells are determinative of the platelet inhibition of said sample.

28. An apparatus as defined in claim 27, wherein the anticoagulant is heparin.

29. An apparatus as defined in claim 28, wherein the amount of heparin in each cell is between about 1 unit and about 3 units per milliliter of blood sample.

30. An apparatus as defined in claim 27, wherein the clotting activator is kaolin.

31. An apparatus as defined in claim 27, wherein the amount of clotting activator in each cell is between about 10 percent and about 12 percent.

32. An apparatus for performing an activated clotting time test on a sample of blood containing platelets using a plunger sensor technique, said apparatus comprising a test cell, and wherein said test cell comprises an anticoagulant, a clotting activator, and a predetermined amount of a platelet inhibitor.